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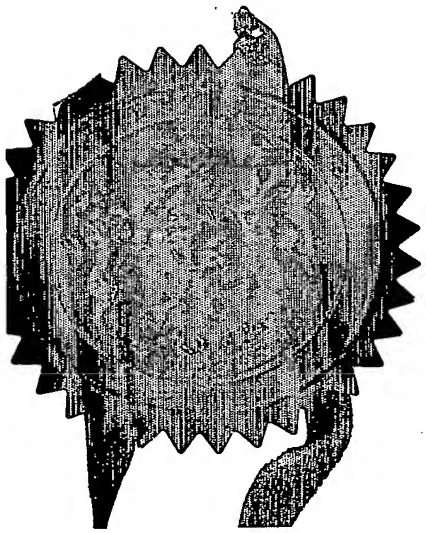

Signed R. Mahoney

Dated 26 September 2002

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23AUG02 E74[redacted]3 D01348
P01/7700 0.[redacted]19687.1

THE PATENT OFFICE
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Request for grant of a patent

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23 AUG 2002

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1. Your reference — P-15579

2. Patent application number *(The Patent Office will fill in this part)* — 0219687.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — ELI LILLY AND COMPANY,
LILLY CORPORATE CENTER,
INDIANAPOLIS,
INDIANA 46285, USA

Patents ADP number *(if you know it)* — 428904002

If the applicant is a corporate body, give the country/state of its incorporation — STATE OF INDIANA, U.S.A.

4. Title of the invention — BENZYL MORPHOLINE DERIVATIVES

5. Name of your agent *(if you have one)* — VAUGHAN, Jennifer Ann

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — LILLY RESEARCH CENTRE,
ERL WOOD MANOR,
WINDLESHAM,
SURREY, GU20 6PH, UK

Patents ADP number *(if you know it)* — 79102760001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
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Description	31
Claim(s)	03
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 23 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom — Georgina L Howard 01276 483443

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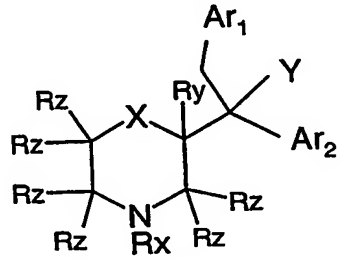
BENZYL MORPHOLINE DERIVATIVES

This invention relates to novel benzyl morpholine compounds, and to their use in selectively inhibiting norepinephrine reuptake.

Selective inhibition of norepinephrine reuptake is a relatively new mode of action for the treatment of affective disorders. Norepinephrine appears to play an important role in the disturbances of vegetative function associated with affective, anxiety and cognitive disorders. Tomoxetine hydrochloride is a selective inhibitor of norepinephrine, and is currently under development for the treatment of attention deficit hyperactivity disorder (ADHD). Reboxetine is a marketed selective norepinephrine reuptake inhibitor for the treatment of depression.

According to the present invention there is provided a compound of formula (I)



(I)

wherein

Rx is H;

Ry is H or C_1-C_4 alkyl;

each Rz is independently H or C_1-C_4 alkyl;

X represents O;

Y represents OH or OR;

R is C_1-C_4 alkyl; and

Ar_1 and Ar_2 are each independently selected from the group consisting of phenyl, and substituted phenyl; and pharmaceutically acceptable salts thereof.

The group Ar_1 may be substituted or unsubstituted phenyl. For example, Ar_1 may be unsubstituted phenyl or, preferably phenyl substituted with 1, 2, 3, 4 or 5 substituents, preferably with 1 or 2, for example 1, substituent. When monosubstituted, the substituted phenyl group is preferably substituted in the 2-

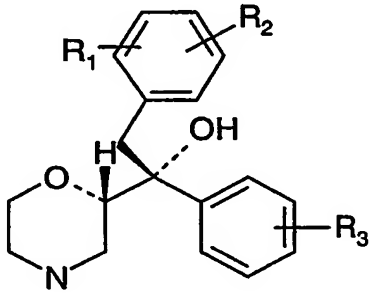
position. Suitable substituents include C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo, and phenyl, optionally substituted with, for example, halo, C_1-C_4 alkyl, or O(C_1-C_4 alkyl).

The group Ar_2 may be substituted or unsubstituted phenyl. For example, Ar_2 may be phenyl substituted with 1, 2, 3, 4 or 5 substituents, preferably with 1 substituent. Suitable substituents include C_1-C_4 alkyl, O(C_1-C_4 alkyl), and especially, halo.

"C_1-C_4 alkyl" as used herein includes straight and branched chain alkyl groups of 1, 2, 3 or 4 carbon atoms, and may be unsubstituted or substituted. C_1-C_2 alkyl groups are preferred. Suitable substituents include halo. Thus the term "C_1-C_4 alkyl" includes haloalkyl. A particularly preferred substituted C_1-C_4 alkyl group is trifluoromethyl.

"Halo" includes F, Cl, Br and I, and is preferably F or Cl.

A preferred group of compounds according to the present invention is represented by the formula (II)



(II)

wherein R_1 and R_2 are each independently selected from H, C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo and phenyl; and

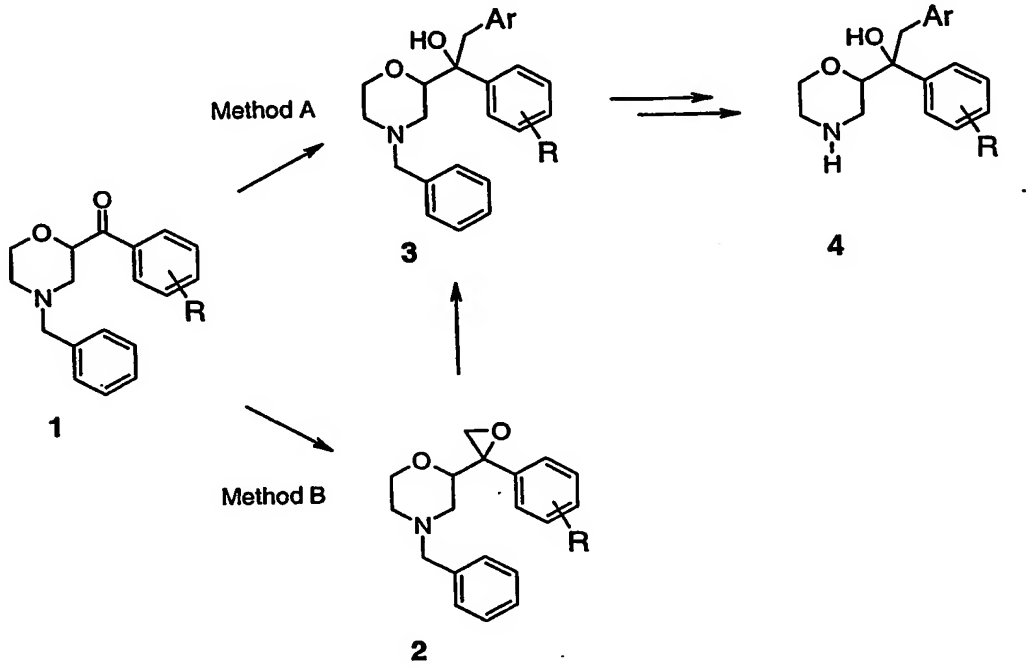
R_3 is selected from H, C_1-C_4 alkyl and halo; and pharmaceutically acceptable salts thereof.

R_1 is preferably C_1-C_3 alkyl, O(C_1-C_3 alkyl), F or Ph. R_2 is preferably H. R_3 is preferably H.

Compounds of the present invention are selective inhibitors of norepinephrine reuptake. In addition, they are acid stable. Advantageously, they have a reduced interation with the liver enzyme CYP2D6. They are indicated for the treatment of disorders associated with norepinephrine dysfunction in mammals.

Compounds of the present invention may be prepared according to the following methods.

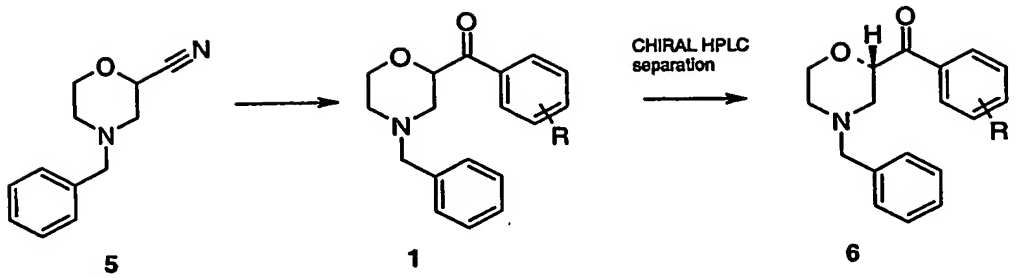
A general scheme outlining the synthetic routes to compounds of the present invention is shown below (**Scheme 1**).



Scheme 1

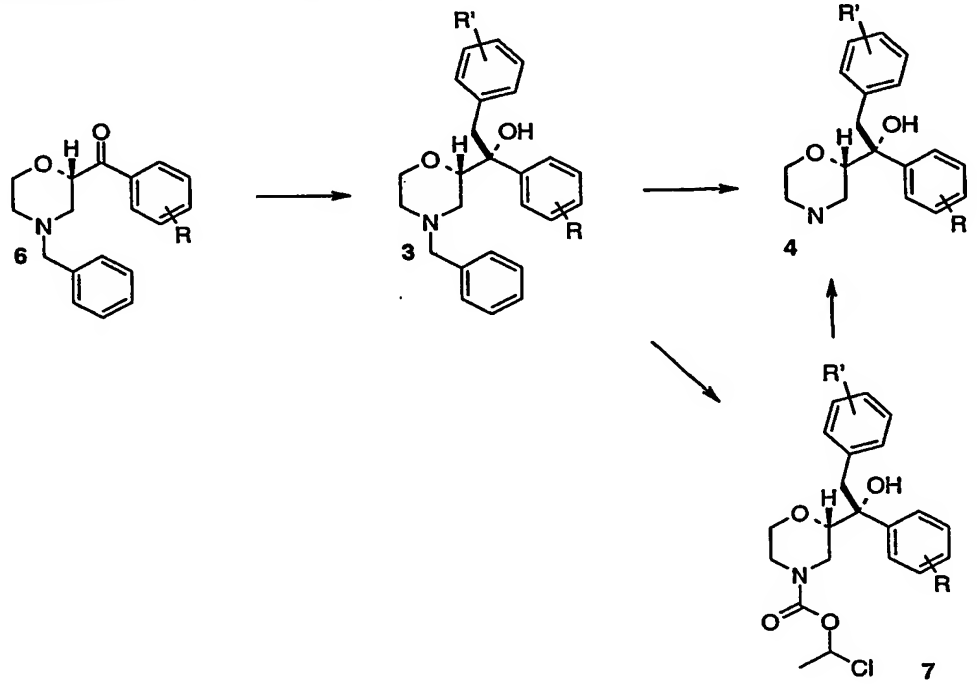
Compounds of the present invention may be prepared by conventional organic chemistry techniques from a *N*-benzyl-ketomorpholine of type **1** by addition of a suitable organometallic derivative (method A), or *via* the addition of a suitable organometallic reagent to an epoxide of type **2** (method B), as outlined in **Scheme 1.**

The racemic intermediates of type **1** may be obtained as outlined in **Scheme 2** by condensation of a *N*-benzyl cyanomorpholine **5** (*J. Med. Chem.* 1993, *36*, pp 683 – 689) with a suitable aryl organometallic reagent followed by acid hydrolysis. Chiral HPLC separations of the racemic *N*-benzyl-aryl-ketomorpholine of type **1** gives the required single enantiomers, i.e., the (2S)- *N*-benzyl-aryl-ketomorpholine of type **6** (**Scheme 2**).



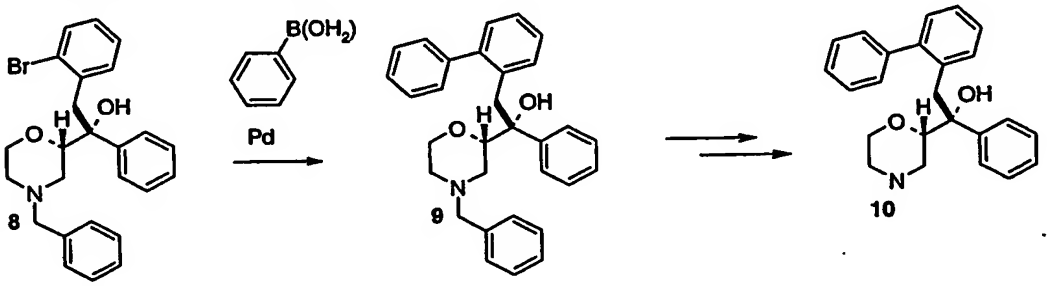
Scheme 2

Condensation of a chiral (2S)-*N*-benzyl-aryl-ketomorpholine of type **6** with a commercially available benzylic magnesium halide or a benzylic magnesium halide prepared using standard Grignard techniques from the corresponding halo-benzylic derivative gives a tertiary alcohols of type **3** without any observed epimerisation of the existing asymmetric center (ee's/de's determinations may be carried out using chiral HPLC) and with very high overall diastereoisomeric excesses (see **Scheme 3**). The final compounds of type **4** may be obtained after cleavage of the *N*-benzyl protecting group on a compound of type **3**. The deprotection can be done using catalytic palladium hydrogenolysis, or carbamate exchange with ACE-Cl (1-Chloroethyl chloroformate), giving intermediates of type **7**, followed by methanolysis as shown in **Scheme 3**.



Scheme 3

The intermediates **3** may be further elaborated using for example organometallic type couplings between an ortho bromide derivative of type **8** and an arylboronic acid as shown in **Scheme 4**.



Scheme 4

An alternative route for the preparation of the compounds of this invention is method B (see **Scheme 1**). Formation of the intermediate epoxides of type **2** from racemic *N*-benzyl-ketomorpholines of type **1**, may be done using for example trimethyl sulfoxonium iodide and a suitable base, for example sodium hydride. Condensation of **2** with a commercially available aryl organometallic, or an aryl organometallic prepared from the corresponding halo aryl derivative, gives the intermediates of type **3**, as mixtures of diastereoisomers. Final deprotections may be done as described above (see scheme **3**). Final compounds made using method B may be purified using chiral HPLC.

In addition to the compounds of formula I and formula II, and processes for the preparation of said compounds, the present invention further provides pharmaceutical compositions comprising a compound of formula I or formula II or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Further, the present invention provides a compound of formula I or formula II or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical; and a compound of formula I or formula II or a pharmaceutically acceptable salt thereof, for use as a selective inhibitor of the reuptake of norepinephrine.

The present compounds and salts may be indicated in the treatment of disorders associated with norepinephrine dysfunction in mammals, including affective, anxiety, and cognitive disorders.

Disorders associated with norepinephrine dysfunction in mammals include, for example, nervous system conditions selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, TIC disorders, cognitive disorders including mild cognitive impairment (MCI), dementia of the Alzheimers type (DAT), vascular dementia and cognitive impairment associated with schizophrenia (CIAS), hypotensive states including orthostatic hypotension, and pain including chronic pain, neuropathic pain and antinociceptive pain. The compounds of the present invention are particularly suitable for the treatment of attention deficit hyperactivity disorder, ADHD.

Thus, the present invention also provides a compound of formula I or formula II for selectively inhibiting the reuptake of norepinephrine; and a compound of formula I or formula II for treating disorders associated with norepinephrine dysfunction in mammals; and the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for selectively inhibiting the reuptake of norepinephrine; and the use of a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of disorders associated with norepinephrine dysfunction in mammals, including the disorders listed herein.

Further, the present invention provides a method for selectively inhibiting the reuptake of norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula I or formula II or a

pharmaceutically acceptable salt thereof; and a method for treating disorders associated with norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula I or formula II or a pharmaceutically acceptable salt thereof.

The present invention includes the pharmaceutically acceptable salts of the compounds of formula I and formula II. Suitable salts include acid addition salts, including salts formed with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic or organic sulphonic acids, for example, acetoxybenzoic, citric, glycolic, *o*- mandelic-l, mandelic-dl, mandelic d, maleic, mesotartaric monohydrate, hydroxymaleic, fumaric, lactobionic, malic, methanesulphonic, napsylic, naphthalenedisulfonic, naphtoic, oxalic, palmitic, phenylacetic, propionic, pyridyl hydroxy pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, 2-hydroxyethane sulphonic, toluene-p-sulphonic, and xinafoic acids.

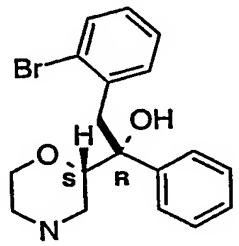
In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

It will be appreciated that compounds of formula I and formula II possess asymmetric carbon atoms, and that in the present invention specific individual stereoisomers are preferred.

The following examples illustrate compounds of the present invention and methods for their preparation.

Stereochemical conventions

The absolute stereochemistry of the compound below was determined using x-ray crystallography.

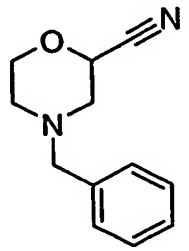


All final compounds were obtained as single isomers either through the use of chirally pure starting materials or chiral separation methods, such as chiral HPLC.

Synthesis of Intermediates.

Preparation of (4-Benzyl-morpholin-2-yl)-phenyl-methanone.

a) 4-Benzyl-morpholine-2-carbonitrile

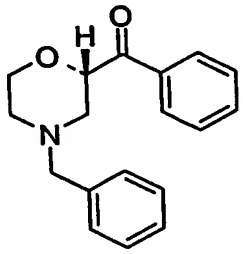


A one-litre reactor with mechanical stirring, cooled by ice bath, was charged with *N*-benzylethanolamine (172.2 g ; 1 equiv.). 2-Chloroacrylonitrile (100 g; 1 equiv.) was added dropwise over 2 minutes. The temperature was maintained between 23 °C and 29 °C by means of the ice bath and subsequently a water bath at 15 °C. *N*-Benzylethanolamine was still detected on TLC after 4.5 h stirring. After one night stirring at room temperature (water bath), no *N*-benzylethanolamine was detectable by ^{1}H RMN. The mixture was dissolved in tetrahydrofuran and transferred to a 2 L reactor cooled to –5 °C by ice/NaCl bath. The total volume of tetrahydrofuran was 1.35 L. Potassium *tert*-butoxyde (148 g; 1.1 equiv.) was added by portions in 1 hour, keeping the reaction temperature at 0±2 °C. After 1 hour post-stirring at 0 °C, the mixture was quenched with saturated $NaHCO_3$ (500 mL). The aqueous layer was extracted with diethyl ether (500 mL). Organic layers were dried on $MgSO_4$ and evaporated to dryness. The title compound (149.8 g; 65%) was obtained after percolation of the 250 g dry residue on 1 kg of SiO_2, eluting with the following gradient:

5% AcOEt – 95% n-heptane	2.5 L
10% AcOEt – 90% n-heptane	2 L
15% AcOEt – 85% n-heptane	2 L

20% AcOEt – 80% n-heptane 5 L

b) (2*S*)-(4-Benzyl-morpholin-2-yl)-phenyl-methanone.

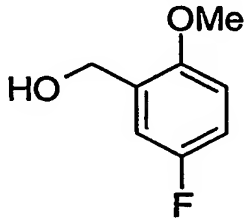


A 3l double jacket reactor was charged with 4-Benzyl-morpholine-2-carbonitrile (135.05 g; 1eq) and dry diethyl ether (1.4 l). When Tj=0°C and Tm=1°C, phenyl magnesium chloride (2M sol. in tetrahydrofuran, 360 ml, 1.08 equiv) was added dropwise over 1hour. Tm rose to 4°C and came back to 2°C at the end of the addition. Tm was progressively raised to 17.5°C over 45 minutes and the mixture stirred at this temperature for another 45 minutes. The reactor was cooled down to Tm=2°C and Tj=0°C (75 minutes) and hydrochloric acid (700ml of 5N solution) was added in two portions. Tm rose to 33°C. After some minutes, the hydrochloride salt of the ketone crystallised. When Tm=Tj=room temperature, the triphasic suspension was filtrated. The organic layer of the mother liquors was eliminated. The filtration cake was then washed with methylene chloride (700 ml). This liquor was charged in the reactor with the acid aqueous layer. Treatment of the hydrochloride salt: After drying under vacuum, 164.4 g of the hydrochloride contaminated with $MgCl_2$ were suspended in a biphasic mixture of water/methylenchloride (500 ml/800 ml). The suspension was basified with aqueous sodium hydroxide (75 ml of a 30% solution) under ice bath cooling. $Mg(OH)_2$ precipitated and the aqueous layer was extracted with methylene chloride. The organic layers were filtrated on a bed of Celite 512 after addition of Celite. The filtrated organic phase was dried over magnesium sulphate and evaporated to dryness. The ketone crystallized readily on standing (132.4 g; 70%). Treatment of the mother liquors: The combined organic phases were washed with aqueous sodium hydroxide (750ml of a 2N solution). Celite 512 (160 g) was added to the suspension which was then filtrated through a bed of Celite. The aqueous layer was

separated and extracted with methylene chloride. The combined organic phases were dried over magnesium sulphate and evaporated to dryness to provide 35.8 g of the title compound enriched with unreacted nitrile. Chiral compound was obtained after separation using chiral HPLC on a Daicel chiralpak AD 20µm column with 100% Ethanol / 0.3% DMEA as eluent at a flow rate of 150ml/min and UV-detection at 300nm.

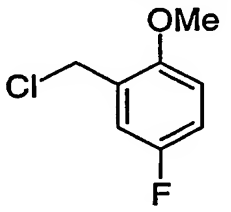
Preparation of 2-Chloromethyl-4-fluoro-1-methoxy-benzene.

a) **(5-Fluoro-2-methoxy-phenyl)-methanol.**



To a solution of 2-Methoxy-5-fluorobenzaldehyde (11.093g, 1 equiv.) in methanol at -10 °C under nitrogen atmosphere was added $NaBH_4$ (7.515g, 2.7 equiv.) portionwise. The solution was allowed to warm to room temperature and after 30 minutes the reaction solvent was removed under reduced pressure and replaced with dichloromethane. This solution was poured onto ice water and further extracted with dichloromethane. The organics fractions were collected and dried ($MgSO_4$) and the solvent removed under reduced pressure to give the title compound as an oil (9.794g, 87%).. ^1H NMR (300MHz, $CDCl_3$): δ 2.58 (m, 1H), 3.81 (s, 3H), 4.63 (d, 2H, J = 6.3 Hz), 6.78 (dd, 1H, J = 8.9 and 4.3 Hz), 6.94 (td, 1H, J = 8.5 and 3.1Hz), 7.04 (dd, 1H, J = 8.7 and 3.1Hz).

b) **2-Chloromethyl-4-fluoro-1-methoxy-benzene.**

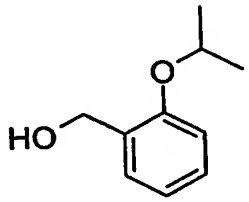


Neat (5-Fluoro-2-methoxy-phenyl)-methanol (19.587g, 1 equiv.) was added to neat $SOCl_2$ (42.2 mL, 4.6 equiv.) at –78°C under a nitrogen atmosphere and the

solution was then allowed to warm to room temperature and stirred until evolution of gas had ceased. An equivalent volume of anhydrous toluene was added to the flask and the solution heated to 60°C. On cooling the reaction solution was poured onto ice water. The toluene layer was separated and dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material was sublimed (60-80°C/0.05 mBarr) to give the title compound as a white solid (13.40 g, 61%). ^{1}H NMR (300MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.60 (s, 2H), 6.79-7.20 (m, 3H).

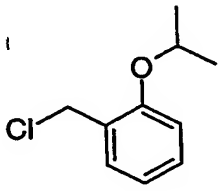
Preparation of 1-Chloromethyl-2-isopropoxy-benzene.

a) (2-Isopropoxy-phenyl)-methanol.



A mixture of 2-hydroxybenzyl alcohol (21.04g, 1 equiv.), 2-isopropyl iodide (32.3 mL, 1.9 equiv.) and K_2CO_3 (71.42g, 3 equiv.) in ethanol was refluxed for 3 hours. On cooling the reaction mixture was filtered and the solvent removed under reduced pressure and replaced with dichloromethane, and then filtered and the solvent removed to give the title compound as an oil (27.751g, 99%). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.37 (d, 6H, J = 6.0Hz), 3.55 (bs, 1H), 4.50-4.70 (m, 3H), 6.78-6.90 (m, 2H), 7.15-7.25 (m, 2H).

b) 1-Chloromethyl-2-isopropoxy-benzene.



The title compound was prepared using the general procedure outlined above for the preparation of 2-Chloromethyl-4-fluoro-1-methoxy-benzene followed by the following treatment:

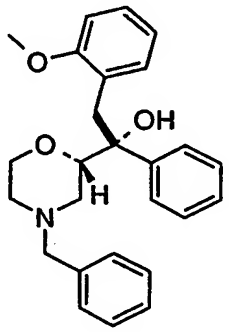
The crude reaction material was chromatographed on silica gel and eluted 1:9 ethyl acetate/heptane prior to distillation (40-60 °C/0.05 mBar). ^{1}H NMR

(300MHz, $CDCl_3$): δ 1.37 (d, 6H, J = 6.0Hz), 4.50-4.70 (m, 3H), 6.80-7.00 (m, 2H), 7.23-7.30 (m, 2H).

Example 1

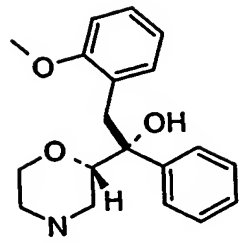
Preparation of (S, R)-2-(2-Methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride.

a) 1-(4-Benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol.



Solid magnesium turnings (9.5 g, 28 equiv.) under nitrogen atmosphere at room temperature were stirred vigorously with a magnetic stirring bar overnight. The magnesium was then covered with dry diethyl ether and to the suspension was added 1,2-dibromoethane (50 µL). A cold bath was then applied followed by dropwise addition of 1-Bromomethyl-2-methoxy-benzene (18.18 g, 5 equiv.) in diethyl ether (71 mL) at a which maintained the temperature at up to 15 °C. The resulting black suspension was stirred at room temperature for 30 minutes and cooled down at –20 °C. A solution of (4-Benzyl-morpholin-2-yl)-phenyl-methanone (4g, 1 equiv.) in diethyl ether (50 mL) was then added dropwise *via canula*. The reaction mixture was left to warm to room temperature over two hours and then quenched by addition of aqueous saturated solution of $NaHCO_3$ (50 mL). The aqueous solution was extracted with diethyl ether, the organic phase dried with $MgSO_4$, evaporated *in vacuo* to give 7 g of a yellow amorphous solid. The compound was taken without further purification in the next step. FIA $[M+H]^+$=404.

b) 2-(2-Methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride.



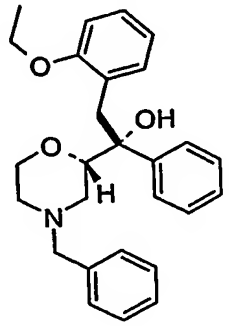
ClH

To a solution of 1-(4-Benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol (1 g, 1 equiv.) in ethyl acetate (100 mL) at room temperature under nitrogen atmosphere was added ammonium formate (3.9 g, 25 equiv.) followed by addition of palladium on charcoal (10 %, 1g.). The reaction mixture was heated to reflux for 1 hour, cooled to room temperature and then filtered through Celite. All volatiles were evaporated under *vacuum*, and the resulting solid was purified via preparative HPLC. The isolated white solid was taken up in ethanol. Hydrogen chloride was added (large excess of 2M solution in diethyl ether) and the mixture was stirred until it became a clear solution. Then all the volatiles were evaporated in vacuo, to give 650 mg of the title compound as white solid (75 %). ^{1}H NMR (300MHz, DMSO D6) δ: 2.43-2.51 (m, 2H), 2.77-2.92 (m, 2H), 3.15-3.23 (m, 3H), 3.41 (s, 3H), 4.10-4.19 (m, 2H), 6.66-6.72 (m, 2H), 6.98-7.07 (m, 2H), 7.13-7.20 (m, 5H), 9.32 (bs, 2H). LCMS (12 minute method) $[M+H]^+$=314 @ Rt 3.96 min. single major peak.

Example 2

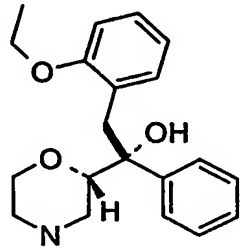
Preparation of (S, R) 2-(2-Ethoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride.

a) **1-(4-Benzyl-morpholin-2-yl)-2-(2-ethoxy-phenyl)-1-phenyl-ethanol.**



The procedure for the synthesis of example **1a**, 1-(4-Benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol, was followed using commercially available 2-ethoxybenzylmagnesium bromide (from Rieke-Metals) as starting material and making non-critical variations, to yield the title compound. FIA $[M+H]^+$=418.

b) 2-(2-Ethoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride.



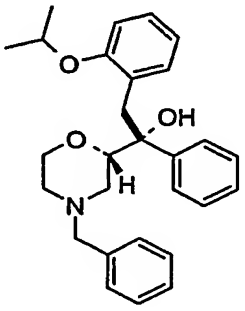
ClH

The procedure for the synthesis of example **1b**, 2-(2-Methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride was followed making non-critical variations, to yield the title compound. ^{1}H NMR (300MHz, DMSO D6) δ: 1.11 (t, 3H, J=6.97Hz), 2.43-2.56 (m, 1H), 2.81-2.96 (m, 2H), 3.17-3.27 (m, 3H), 3.55-3.67 (m, 2H), 3.84-3.92 (m, 1H), 4.05-4.20 (m, 2H), 6.68-6.74 (m, 2H), 7.01-7.18 (m, 8H), 8.92 (bs, 2H) ppm. LCMS (12 minute method) $[M+H]^+$=328 @ Rt 4.57 min. single major peak.

Example 3

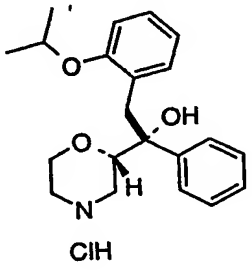
Preparation of (S, R) 2-(2-Isopropoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride.

a) 1-(4-Benzyl-morpholin-2-yl)-2-(2-isopropoxy-phenyl)-1-phenyl-ethanol.



Solid magnesium turnings (4.6 g, 48 equiv.) under nitrogen atmosphere at room temperature were stirred vigorously with a magnetic stirring bar overnight. The magnesium was then covered with dry tetrahydrofuran. A cold bath was then applied followed by dropwise addition of 1-chloromethyl-2-isopropoxy-benzene (3.0 g, 4 equiv.) in tetrahydrofuran (40 mL). During slow addition of the electrophile no exotherm was observed so on completion of addition 3 crystals of Iodine were added to promote initiation of the reaction. After this addition the reaction temperature was allowed to spike to 50 °C then cooled rapidly to 8 °C before being left to warm to room temperature for one hour. The resulting black suspension was cooled down to –10 °C and a solution of (4-Benzyl-morpholin-2-yl)-phenyl-methanone (1.2 g, 1 equiv.) in tetrahydrofuran (10 mL) was then added dropwise. The reaction mixture was left to warm to room temperature over thirty minutes and then quenched by addition of aqueous saturated solution of $NaHCO_3$ (50 mL) prior to filtration through Celite. The aqueous solution was extracted with diethyl ether, the organic phase dried with $MgSO_4$, evaporated *in vacuo* to give 3 g of a yellow amorphous solid. The compound was taken without further purification in the next step. LCMS (6 minutes method) $[M+H]^+$=432 @ Rt 3.25 min. major peak.

b) 2-(2-Isopropoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride.



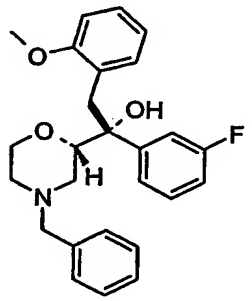
The procedure for the synthesis of example **1b**, 2-(2-Methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride was followed making non-critical variations, to yield the title compound. ^1H NMR (300MHz, MeOH D3) δ: 1.12-1.16 (m, 6H), 2.51-2.55 (m, 1H), 2.89-3.14 (m, 4H), 3.56-3.60 (m, 1H), 3.82-3.92 (m,

1H), 3.99-4.03 (m, 1H), 4.17-4.22 (m, 1H), 4.36-4.44 (m, 1H), 6.50-6.55 (m, 1H), 6.66-6.73 (m, 2H), 6.92-6.98 (m, 1H), 7.07-7.20 (m, 5H) ppm. LCMS (12 minutes method) $[M+H]^+$= 342 @ Rt 4.90 min. major peak.

Example 4

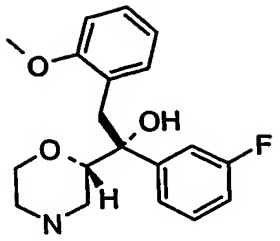
Preparation of (S, R) 1-(3-Fluoro-phenyl)-2-(2-methoxy-phenyl)-1-morpholin-2-yl-ethanol hydrochloride

a) 1-(4-Benzyl-morpholin-2-yl)-1-(3-fluoro-phenyl)-2-(2-methoxy-phenyl)-ethanol.



A magnetically stirred 0.25M tetrahydrofuran solution of commercially available 2-methoxybenzylmagnesium bromide (from Rieke-Metals) (80ml, 3equiv.) under nitrogen atmosphere was cooled to -10 °C and to this was added neat (4-Benzyl-morpholin-2-yl)-1-(3-fluoro-phenyl)-methanone (2.1g, 1equiv.). The solution was allowed to warm to room temperature and reaction progress followed using mass spectrometry. After 1.5 hours 2-methoxybenzylmagnesium bromide solution (14ml, 0.5equiv.) was again added to the reaction and after a further 0.5 hours an aqueous saturated solution of $NaHCO_3$ (50 mL) was added to halt the reaction. The aqueous solution was extracted with diethyl ether, the organic phase dried with $MgSO_4$, evaporated *in vacuo* to give 2.8 g of a yellow amorphous solid. The compound was taken without further purification in the next step.
LCMS (6 minutes method) $[M+H]^+$=422 @ Rt 3.03 and 2.86 min. major peaks.

b) (S, R)-1-(3-Fluoro-phenyl)-2-(2-methoxy-phenyl)-1-morpholin-2-yl-ethanol hydrochloride.



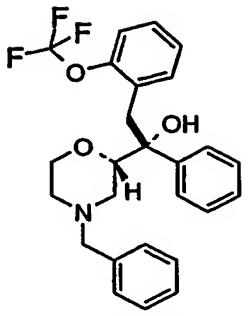
ClH

To a solution of 1-(4-Benzyl-morpholin-2-yl)-1-(3-fluoro-phenyl)-2-(2-methoxy-phenyl)-ethanol (2.8 g, 1 equiv.) in ethyl acetate (100 mL) at room temperature under nitrogen atmosphere was added ammonium formate (4.3 g, 10 equiv.) followed by addition of palladium on charcoal (10 %, 2.7g.). The reaction mixture was heated to reflux for 1 hour, cooled to room temperature and then filtered through Celite. All volatiles were evaporated under *vacuum*, and the resulting solid was purified via preparative HPLC to give the desired diastereoisomers. The active enantiomer was obtained after a further preparative chiral HPLC separation. The active enantiomer, a white solid, was next taken up in ethanol and hydrogen chloride was added (large excess of 2M solution in diethyl ether) and the mixture was stirred until it became a clear solution. Then all the volatiles were evaporated in vacuo, to give 447mg of the title compound as white solid. ^{1}H NMR (300MHz, DMSO D6) δ: 2.49-2.53 (m, 1H), 2.80-2.93 (m, 2H), 3.12-3.33 (m, 4H), 3.41 (s, 3H), 3.85-3.92 (m, 1H), 4.07-4.20 (m, 2H), 6.70-6.75 (m, 2H), 6.92-7.10 (m, 5H), 7.20-7.27 (m, 1H), 9.08 (bs, 2H). LCMS (12 minutes method) $[M+H]^+$=332. Rt 4.11min.

Example 5

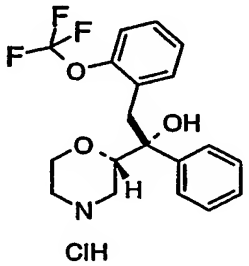
Preparation of (S, R) 1-Morpholin-2-yl-1-phenyl-2-(2-trifluoromethoxy-phenyl)-ethanol hydrochloride

a) 1-(4-Benzyl-morpholin-2-yl)-1-phenyl-2-(2-trifluoromethoxy-phenyl)-ethanol.



The procedure for the synthesis of example **1a**, 1-(4-Benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol, was followed using 2-(trifluoromethoxy)benzyl bromide (from Fluorochem) as starting material and making non-critical variations, to yield the title compound. FIA $[M+H]^+$=458.

b) (S, R) 1-Morpholin-2-yl-1-phenyl-2-(2-trifluoromethoxy-phenyl)-ethanol hydrochloride.



ClH

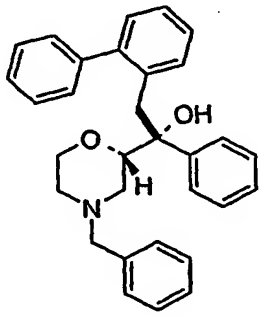
To a solution of 1-(4-Benzyl-morpholin-2-yl)-1-phenyl-2-(2-trifluoromethoxy-phenyl)-ethanol (7 g, 1 equiv.) in dry 1,2-dichloroethane (40 mL) at 0 °C under nitrogen atmosphere was added ACE-Cl (20.33 g, 10 equiv.). The reaction mixture was left to warm to room temperature for 48 hours. All volatiles were evaporated under vacuum, and the resulting solid was taken-up with methanol (50 mL) and stirred at room temperature overnight. The solution was filtered through acid ion exchange column and the required fractions evaporated to dryness. The resulting solid was taken up with acetonitrile and the insoluble material filtered off. The mother liquor was concentrated in vacuo and purified via preparative HPLC. Both fractions were mixed (from slurry and from HPLC) and taken up in ethanol. Hydrogen chloride was added (large excess of 2M solution in diethyl ether) and the mixture stirred. Then all the volatiles were evaporated in vacuo, to give 1.9 g of the title compound as a white solid (33 %). ^{1}H NMR (300MHz, DMSO D6) δ: 2.45-2.50 (m, 1H), 2.81-2.97 (m, 2H), 3.18-3.30 (m, 3H), 3.89-3.97 (m, 1H), 4.15-

4.18 (m, 2H), 7.02-7.29 (m, 9H), 9.18 (bs, 2H). LCMS (12 minutes method) $[M+H]^+$=368 @ Rt 4.88 min. single major peak.

Example 6

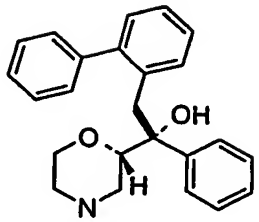
Preparation of (S, R) 2-Biphenyl-2-yl-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride

a) 1-(4-Benzyl-morpholin-2-yl)-2-biphenyl-2-yl-1-phenyl-ethanol.



1-(4-Benzyl-morpholin-2-yl)-2-(2-bromo-phenyl)-1-phenyl-ethanol (0.50 g, 1.0 equiv.) and boronic acid (0.402 g, 3.0 equiv.) were suspended in a mixture ethanol/water (2/1, 7.5 mL) and $Pd(Ph_3)_4$ (0.022 g, 0.04 equiv.), then K_2CO_3 (0.654 g, 4.30 equiv.) were added. The mixture was heated to 80°C under nitrogen atmosphere. After 16 hours, the reaction was cooled down to room temperature and filtered through Celite, then extracted with ethyl acetate. The organic layers were combined, dried with $MgSO_4$, filtered and concentrated in vacuo yielding a yellow oil, which was purified by column chromatography on silica gel (10% EtOAc:Hexane) to give 0.491g (98%) of the title compound as a white solid.

b) (S, R) 2-Biphenyl-2-yl-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride.



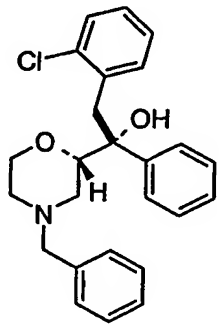
ClH

The procedure for the synthesis of example 1, 2-(2-methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride, was followed making non-critical variations, to yield the title compound. ^{1}H NMR (300MHz, DMSO D6) δ: 2.16-2.20 (m, 1H), 2.54-2.62 (m, 1H), 2.67-2.76 (m, 1H), 2.85-2.89 (m, 1H), 3.24 (s, 2H), 3.61-3.69 (m, 2H), 3.93-3.98 (m, 1H), 5.14 (bs, 1H), 6.80-6.92 (m, 5H), 7.04-7.17 (m, 5H), 7.27-7.30 (m, 3H), 7.36-7.39 (m, 1H). LCMS (12 minutes method) $[M+H]^+$=360 @ Rt 5.15 min. single major peak.

Example 7

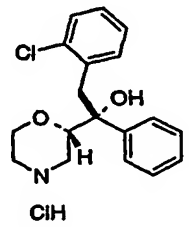
Preparation of (S, R) 2-(2-Chloro-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride

a) **1-(4-Benzyl-morpholin-2-yl)-2-(2-chloro-phenyl)-1-phenyl-ethanol.**



The procedure for the synthesis of example **1a**, 1-(4-Benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol, was followed using 2-cholobenzyl chloride (from Aldrich) as starting material and making non-critical variations, to yield the title compound. FIA $[M+H]^+$=408 and 410.

b) (S, R) 2-(2-Chloro-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride

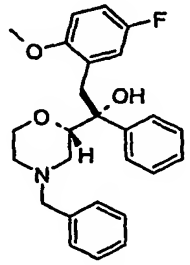


The procedure for the synthesis of example 5b, (S, R) 1-Morpholin-2-yl-1-phenyl-2-(2-trifluoromethoxy-phenyl)-ethanol hydrochloride, was followed making non-critical variations, to yield the title compound. ^{1}H NMR (300MHz, DMSO D6) δ: 2.45-2.54 (m, 1H), 2.84-2.93 (m, 2H), 3.17-3.22 (m, 1H), 3.33-3.38 (m, 3H), 3.89-3.97 (m, 1H), 4.14-4.18 (m, 2H), 7.06-7.11 (m, 2H), 7.15-7.26 (m, 7H), 9.24 (bs, 2H) ppm. LCMS (12 minutes method) $[M+H]^+$=318-320 @ Rt 4.36 min. single peak.

Example 8

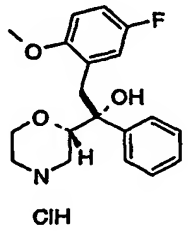
Preparation of (S, R) 2-(5-Fluoro-2-methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride

a) 1-(4-Benzyl-morpholin-2-yl)-2-(5-fluoro-2-methoxy-phenyl)-1-phenyl-ethanol.



The procedure for the synthesis of example **1a**, 1-(4-Benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol, was followed making non-critical variations, to yield the title compound which was taken without further purification in the next step. LCMS (6 minutes method) $[M+H]^+$=422 @ Rt 2.85 min. major peak.

b) (S, R) 2-(5-Fluoro-2-methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride

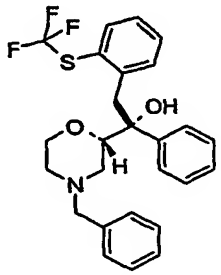


The procedure for the synthesis of **1b**, 2-(2-Methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride was followed making non-critical variations, to yield the title compound. ^{1}H NMR (300MHz, DMSO D6) δ: 2.44-2.50 (m, 1H), 2.79-2.96 (m, 2H), 3.15-3.20 (m, 2H), 3.27-3.33 (m, 2H), 3.42 (s, 3H), 3.86-3.94 (m, 1H), 4.09-4.18 (m, 2H), 6.66-6.71 (m, 1H), 6.80-6.90 (m, 2H), 7.14-7.23 (m, 5H), 9.20 (bs, 2H).LCMS (12 minutes method) $[M+H]^+$=332.

Example 9

Preparation of (S, R) 1-Morpholin-2-yl-1-phenyl-2-(2-trifluoromethylsulfanyl-phenyl)-ethanol acetate

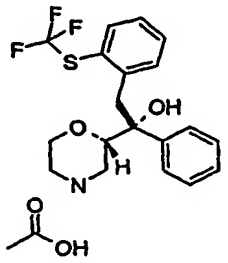
a) 1-(4-Benzyl-morpholin-2-yl)-1-phenyl-2-(2-trifluoromethylsulfanyl-phenyl)-ethanol.



The procedure for the synthesis of example **1a**, 1-(4-benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol, was followed using 1-bromomethyl-2-trifluoromethylsulfanyl-benzene as starting material and making non-critical variations, to yield the title compound. ^{1}H NMR (300MHz, $CDCl_3$) δ: 2.05-2.33 (m, 3H), 2.49-2.65 (m, 1H), 3.10-3.35 (m, 2H), 3.43-3.55 (m, 1H), 3.67-3.89 (m, 2H),

3.91-4.08 (m, 2H), 4.09-4.22 (m, 1H), 6.91-7.05 (m, 1H), 7.10-7.42 (m, 7H), 7.50-7.63 (m, 1H) ppm.

b) (S, R) 1-Morpholin-2-yl-1-phenyl-2-(2-trifluoromethylsulfanyl-phenyl)-ethanol acetate

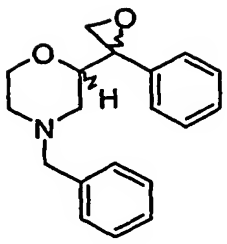


To a solution of 1-(4-benzyl-morpholin-2-yl)-1-phenyl-2-(2-trifluoromethylsulfanyl-phenyl)-ethanol (218 mg g, 1 equiv.) and solid supported Hunig's base (from Argonaut, 1g, 5 equiv.) in dry tetrahydrofuran (4 mL) at 0 °C under nitrogen atmosphere was added ACE-Cl (502 µL, 10 equiv.). The reaction mixture was left to warm to room temperature for 48 hours. All volatiles were evaporated under vacuum, and the resulting solid was taken-up with methanol (50 mL) and stirred at room temperature overnight. The solution was filtered through acid ion exchange column and the required fractions evaporated to dryness. The resulting solid was purified *via* preparative HPLC to give 62 mg of the title compound as a colourless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ: 2.01 (s, 3H), 2.43-2.47 (m, 1H), 2.63-2.70 (m, 1H), 2.81-2.94 (m, 2H), 3.24 (d, 1H, J=13.57Hz), 3.85-3.96 (m, 2H), 4.01-4.05 (m, 1H), 4.09-4.13 (m, 1H), 4.45 (bs, 4H), 6.90-6.93 (m, 1H), 7.13-7.26 (m, 7H), 7.55-7.58 (m, 1H) ppm. LCMS (12 minute method) $[M+H]^+$=384 @ Rt 5.13 min. single peak.

Example 10

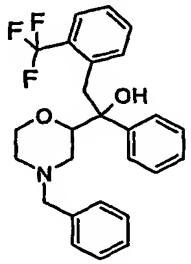
Preparation of (S, R) 1-Morpholin-2-yl-1-phenyl-2-(2-trifluoromethyl-phenyl)-ethanol

a) 4-Benzyl-2-(2-phenyl-oxiranyl)-morpholine.



To a mixture of trimethylsulfoxonium iodide (783 mg, 1equiv.) and sodium hydride (142 mg, 1 equiv.) in dimethylformamide (17 mL) at 0 °C under nitrogen atmosphere was added dimethylsulfoxide (251 μL, 1 equiv.) and the resulting suspension was stirred for 30 minutes. A solution of (4-Benzyl-morpholin-2-yl)-phenyl-methanone (1 g, 1equiv.) in dimethylformamide (10 mL) was then added dropwise. Stirring was continued for 30 minutes and the reaction was stopped by addition of water (50 mL). The aqueous solution was extracted with diethyl ether, the organic phase dried with $MgSO_4$, and evaporated *in vacuo*. The crude material was purified using a column chromatography on silica gel eluting with a mixture of ethyl acetate/heptane (20/80) to give 825 mg of the title compound as a colourless oil (78 %), mixture of two diastereoisomers.

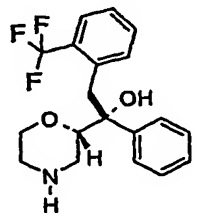
b) 1-(4-Benzyl-morpholin-2-yl)-1-phenyl-2-(2-trifluoromethyl-phenyl)-ethanol.



To a suspension of magnesium turnings in tetrahydrofuran (2mL) at room temperature under nitrogen atmosphere was added a solution 1-Bromo-2-trifluoromethyl-benzene (7.6g, 5equiv.) in tetrahydrofuran (32 mL) and the mixture was stirred for an hour. The solution was cooled to –78 °C and copper iodide (646 mg) was added followed by dropwise addition of a solution of 4-Benzyl-2-(2-phenyl-oxiranyl)-morpholine (2g, 1 equiv.) in tetrahydrofuran (10 mL). The resulting mixture was warmed to room temperature over 2 hours and then treated

with water (10 mL). The solution was extracted with diethyl ether, the organic phase dried with $MgSO_4$, and evaporated *in vacuo*. The crude material was purified using a column chromatography on silica gel eluting with a mixture of ethyl acetate/heptane (10/90) to give 352 mg of the title compound as a colourless oil (12 %). LCMS (6 minutes method) $[M+H]^+$=442 @ Rt 3.05 min. major peak.

c) (S, R) 1-Morpholin-2-yl-1-phenyl-2-(2-trifluoromethyl-phenyl)-ethanol

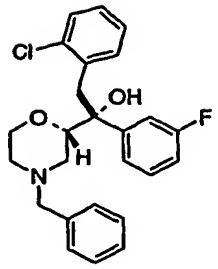


To a solution of 1-(4-Benzyl-morpholin-2-yl)-1-phenyl-2-(2-trifluoromethyl-phenyl)-ethanol (352 mg, 1 equiv.) in ethanol (15 mL) at room temperature under nitrogen atmosphere was added ammonium formate (507 mg g, 10 equiv.) followed by addition of palladium on charcoal (10 %, 355 mg.). The reaction mixture was heated to reflux for 1 hour, cooled to room temperature and then filtered through Celite. All volatiles were evaporated under vacuum to give 265 mg of the title compound as white solid (94 %). The enantiomeric mixture was resolved using chiral HPLC, to give the title compound as a single enantiomer. ^1H NMR (300MHz, $CDCl_3$) δ: 1.62 (bs, 4H), 2.25-2.30 (m, 1H), 2.56-2.64 (m, 1H), 2.75-2.87 (m, 2H), 3.18 (d, 1H, J=14.88Hz), 3.71-3.81 (m, 2H), 3.89 (d, 1H, J=14.88Hz), 4.02-4.05 (m, 1H), 6.83-6.86 (m, 1H), 7.09-7.34 (m, 7H), 7.53-7.55 (m, 1H) ppm. LCMS (12 minute method) $[M+H]^+$=352 @ Rt 4.73 min. single peak.

Example 11

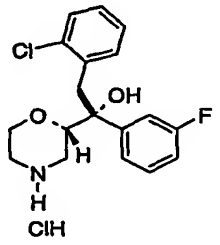
Preparation of (S, R) 2-(2-Chloro-phenyl)-1-(3-fluoro-phenyl)-1-morpholin-2-yl-ethanol hydrochloride

a) 1-(4-Benzyl-morpholin-2-yl)-2-(2-chloro-phenyl)-1-(3-fluoro-phenyl)-ethanol.



The procedure for the synthesis of **4a**, 1-(4-Benzyl-morpholin-2-yl)-1-(3-fluoro-phenyl)-2-(2-methoxy-phenyl)-ethanol was followed using 2-chorobenzyl chloride as starting material, and making non-critical variations, to yield the title compound which was taken without further purification in the next step. LCMS (6 minutes method) $[M+H]^+$=426 @ Rt 2.85 min. major peak.

b) (S, R) 2-(2-Chloro-phenyl)-1-(3-fluoro-phenyl)-1-morpholin-2-yl-ethanol hydrochloride



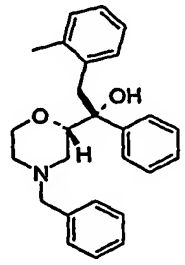
To a solution of 1-(4-Benzyl-morpholine-2-yl)-2-(2-chloro-phenyl)-1-(3-fluoro-phenyl)-ethanol. (3.2g, 1 equiv.) in dry 1,2-dichloroethane (40 mL) under nitrogen atmosphere was added ACE-Cl (20.33 g, 5 equiv.). The reaction mixture was stirred at room temperature overnight then refluxed until completion. All volatiles were evaporated under vacuum, and the resulting residue redissolved in acetonitrile. This solution was filtered through an ion exchange column and the filtrate taken-up with methanol (50 mL) and refluxed for 3h. The solution was again filtered through acid ion exchange column and the required fractions evaporated to dryness. The resulting solid was next purified via preparative HPLC followed by chiral HPLC. The purified active enantiomer was taken up in ethanol and hydrogen chloride was added (large excess of 2M solution in diethyl ether) and the mixture stirred. Then all the volatiles were evaporated in vacuo, to give 519mg of the title compound as a white solid (18 %). ^{1}H NMR (300MHz, DMSO D6) δ: 2.43-2.54

(m, 1H), 2.81-2.95 (m, 2H), 3.16-3.23 (m, 1H), 3.30-3.44 (m, 2H), 3.54 (bs, 1H), 3.92-4.00 (m, 1H), 4.15-4.23 (m, 2H), 6.96-7.29 (m, 8H), 9.32-9.45 (m, 2H).LCMS (12minute method) $[M+H]^+$=336.

Example 12

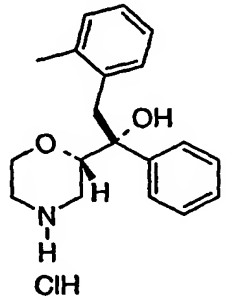
Preparation of (S, R) 1-Morpholin-2-yl-1-phenyl-2-*o*-tolyl-ethanol hydrochloride

a) 1-(4-Benzyl-morpholin-2-yl)-1-phenyl-2-*o*-tolyl-ethanol.



The procedure for the synthesis of example **1a**, 1-(4-benzyl-morpholin-2-yl)-2-(2-methoxy-phenyl)-1-phenyl-ethanol, was followed using commercially available 2-methylbenzylmagnesium bromide (from Rieke-Metals) as starting material and making non-critical variations, to yield the title compound. FIA $[M+H]^+$= 388.

b) (S, R) 1-Morpholin-2-yl-1-phenyl-2-*o*-tolyl-ethanol hydrochloride



The procedure for the synthesis of example **1b**, 2-(2-methoxy-phenyl)-1-morpholin-2-yl-1-phenyl-ethanol hydrochloride was followed making non-critical variations, to yield the title compound. ^{1}H NMR (300MHz, DMSO D6) δ: 1.62 (s, 3H), 2.40-2.58 (m, 1H), 2.78-3.01 (m, 2H), 3.03-3.09 (m, 1H), 3.15-3.31 (m, 2H),

3.90-4.05 (m, 1H), 4.15-4.25 (m, 2H), 6.89-7.28 (m, 9H), 9.21-9.55 (m, 2H). LCMS $[M+H]^+$=298 single peak.

The compounds of the present invention may be used as medicaments in human or veterinary medicine. The compounds may be administered by various routes, for example, by oral or rectal routes, topically or parenterally, for example by injection, and are usually employed in the form of a pharmaceutical composition.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. Where the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

Some examples of suitable carriers are lactose, dextrose, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as starch and petroleum jelly, sucrose sorbitol, mannitol, starches, gum acacia,calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl- hydrobenzoate, talc, magnesium stearate and mineral oil. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins. Compositions of the invention may be formulated so as to provide, quick, sustained or delayed release of

the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The pharmacological profile of the present compounds may be demonstrated as follows.

Scintillation proximity assays for determining the affinity of test ligands at the norepinephrine transporter.

The compounds of the invention are norepinephrine reuptake inhibitors, and possess excellent activity in, for example, a scintillation proximity assay (e.g. J. Gobel, D.L. Saussy and A. Goetz, J. Pharmacol. Toxicolo. (1999), 42, 237-244). Thus ^{3}H-nisoxetine binding to norepinephrine re-uptake sites in a cell line transfected with human norepinephrine transporter binding has been used to determine the affinity of ligands at the norepinephrine transporter.

Acid Stability

The acid stability of a compound according to the present invention was determined as a solution in buffer at 6 different pH values (HCl0.1N, pH 2, pH 4, pH 6, pH 7, and pH 8) at 40°C over a time course of 72 hours. Samples were taken at the beginning of the study and after 3, 6 and 24 hours and analysed by capillary electrophoresis. The original sample used in this study contained 0.8% of the undesired epimer as internal standard. The samples taken at the different time points during the study did not show any significant change in the percentage of the undesired epimer. This confirms that the compound is chemically and configurationally stable under acidic conditions.

In Vitro Determination of the Interaction of compounds with CYP2D6 in Human Hepatic Microsomes

Principle:

The interaction of compounds with CYP2D6 was evaluated by the measurement of the inhibition of the bufurolol 1'-hydroxylase activity by the compounds.

Assay description:

Bufuralol 1-hydroxylase activity is determined by using 0.5 mg/ml human liver microsomal protein (human biologics), 10 μmol/L bufuralol, in 0.1 M sodium phosphate buffer pH 7.4, incubated for 5 min at 37°C in the presence of 2 mM βNADPH, with 0, 5 or 25 μM of the test compound (inhibitor). The compound was dissolved in acetonitrile, such that the final concentration of acetonitrile in the incubation was 0.5%. The total reaction volume was 100 μl. The reaction was terminated by addition of 75 μl of methanol followed by centrifugation. 40 μl of the supernatant was analysed by HPLC.

Analysis conditions:

A Beckman Ultrasphere C_{18} column (5 μm, 250 x 4.6 mm) was used, with a 13 minute gradient from 100% of solvent A (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (65/35)) to 100 % of solvent B (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (20/80)), according to the following gradient. The run time was 20 minutes. Formation of 1'-hydroxybufuralol was detected by fluorimetric detection with extinction at λ 252 nm and emission at λ 302 nm.

Time (min)	Solvent A (%)	Solvent B (%)
0	100	0
8	0	100
12	0	100
13	100	0

Calculation of the results:

The percent of inhibition is calculated as follows:

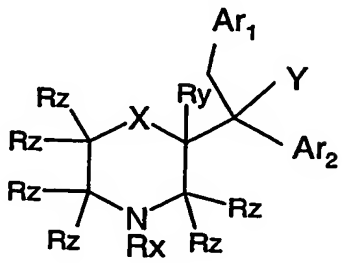
$$100 - \frac{100 \times \text{1'-hydroxybufuralol area formed with inhibitor}}{\text{1'-hydroxybufuralol area formed without inhibitor}}$$

The IC_{50} is calculated from the percent inhibition as follows (assuming competitive inhibition): $\frac{\text{Compound Concentration} \times (100 - \text{Percent of inhibition})}{\text{Percent of inhibition}}$

The IC_{50} estimation is assumed valid if inhibition is between 20% and 80% (Moody 1999).

CLAIMS

1. A compound of formula (I)



(I)

wherein

Rx is H;

Ry is H or C_1-C_4 alkyl;

each Rz is independently H or C_1-C_4 alkyl;

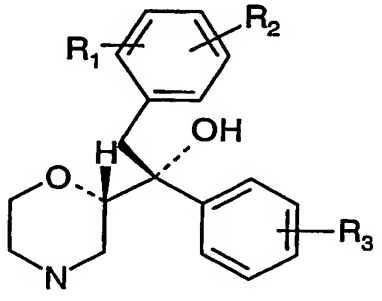
X represents O;

Y represents OH or OR;

R is C_1-C_4 alkyl; and

Ar_1 and Ar_2 are each independently selected from the group consisting of phenyl, and substituted phenyl; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, represented by the formula II



(II)

wherein R_1 and R_2 are each independently selected from H, C_1-C_4 alkyl, O(C_1-C_4 alkyl), S(C_1-C_4 alkyl), halo and phenyl; and

R_3 is selected from H and C_1-C_4 alkyl; and pharmaceutically acceptable salts thereof.

3. A compound as claimed in claim 2, wherein R_1 is selected from C_1-C_4 alkyl, O(C_1-C_4 alkyl), F and Ph.

4. A compound as claimed in claim 3, wherein R_2 is H.

5. A compound as claimed in claim 4, wherein R_3 is H.

6. A compound as claimed in any one of claims 1-5, for use as a pharmaceutical.

7. A compound as claimed in any one of claims 1-5, for use as a selective inhibitor of the reuptake of norpinephrine.

8. The use of a compound as claimed in any one of claims 1-5, for treating a disorder associated with norepinephrine dysfunction in mammals.

9. The use of a compound as claimed in any one of claims 1-5, for the manufacture of a medicament for treating a disorder associated with norepinephrine dysfunction in mammals.

10. A method for selectively inhibiting the reuptake of norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1-5, or a pharmaceutically acceptable salt thereof.

11. a method for treating disorders associated with norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1-5, or a pharmaceutically acceptable salt thereof.

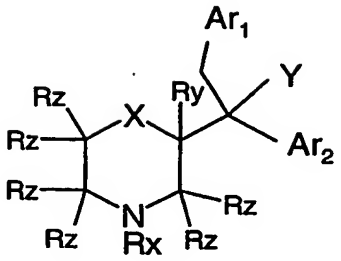
12. A method or use as claimed in any one of claims 8, 9 and 11, wherein the disorder is selected from nervous system conditions selected from the

group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, TIC disorders, cognitive disorders including mild cognitive impairment (MCI), dementia of the Alzheimers type (DAT), vascular dementia and cognitive impairment associated with schizophrenia (CIAS), hypotensive states including orthostatic hypotension, and pain including chronic pain, neuropathic pain and antinociceptive pain.

13. A method or use as claimed in any one of claims 8, 9 and 11, wherein the disorder is attention deficit hyperactivity disorder, ADHD.

ABSTRACT

A compound of formula (I)



(I)

wherein

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Ry is H or C_1-C_4 alkyl;

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X represents O;

Y represents OH or OR;

R is C_1-C_4 alkyl; and

Ar_1 and Ar_2 are each independently selected from the group consisting of phenyl, and substituted phenyl; and pharmaceutically acceptable salts thereof.